REMARKS

Amendments to the Claims

Claim 77 has been cancelled without prejudice or disclaimer, and claims 39-42, 44, 46-48, 55-58, 66, 67, 74-76 and 78 have been amended. The amended claims are fully supported by the specification and by the claims as originally filed. Following entry of the claim amendments presented above, claims 39-44, 46-58 and 78 are pending and claims 60-66, 67, 70 and 74-76 have been withdrawn from further consideration. Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks.

In the October 6, 2009, Office Action, claims 39-44, 46-58 and 77-78 were rejected under 35 USC §112, second paragraph, as allegedly indefinite, and under §112, first paragraph, for alleged lack of written description and enablement. The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejection Under 35 U.S.C.§ 112, Second Paragraph

Claims 39-44, 46-58 and 77-78 are rejected as allegedly indefinite. Specifically, the Examiner asserts that the relationship between an immune response of a "different quality" and selecting a synonymous codon on the basis that it has a "different preference" for an immune responses is unclear. In particular, the Examiner asserts that the "different quality" refers to the same immune response in which the "quality" of the immune response is different with respect to the synthetic polynucleotide in comparison to the parent polynucleotide and that the "different preference" refers to different immune responses entirely. Applicant respectfully traverses.

Applicant respectfully submits that the scope and meaning of the rejected claims are clear to one skilled in the art, and that the claims fully comply with §112, second paragraph. Nevertheless, without acquiescing in the propriety of the rejection, and while reserving the right to pursue the claims in the form previously presented, applicant has amended the claims to expedite favourable prosecution. In particular, claim 39 and its dependent claims are amended to recite that the immune response is of a selected class. The instant specification contemplates various phenotypes, for example, in paragraph [0061], including with respect to immune responses, immunity (*e.g.*, immunity to pathogenic infection or cancer) and antigen tolerance (*e.g.*, antigen-specific T-lymphocyte antigen, tolerance to allergens, transplantation antigens and self antigens) (*see*, in particular, page 14, lines 30-32). Determination of codon

preferences for subclasses of immunity is also contemplated in the specification (*see*, in particular, page 15, lines 24-29) including innate immunity (which can be further subdivided *inter alia* into complement system, monocytes, macrophages, neutrophils and natural killer cells), cellular immunity (which can be further subdivided *inter alia* into cytolytic T-lymphocytes, dendritic cells and T-helper lymphocytes) and humoral immunity (which can be further subdivided *inter alia* into antibody subclasses IgA, IgD, IgE, IgG, and IgM).

Claim 39 also has been amended to refer to the "strength, intensity or grade" in the context of conferring an immune response of the selected class. It is apparent, therefore, that the comparison of immune response preferences recited in step (a) of claim 39 refers to a ranking of synonymous codons based on their preference for conferring an immune response of the selected class (*e.g.*, conferring a humoral immune response). It is apparent, therefore, that replacing codons of a polynucleotide of interest with codons that have a higher preference for conferring an immune response of the selected class (*e.g.*, a humoral response), will generally confer an immune response of the selected class in a higher strength, intensity or grade that that conferred by the polynucleotide of interest prior to codon optimization.

Applicant respectfully submits that the claims fully comply with the requirements of §112, second paragraph, and respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C.§ 112 First Paragraph (Written Description)

Claims 39-44, 46-58 and 77-78 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Specifically, the Examiner asserts that applicant lacks possession of the claimed invention asserts because the metes and bounds of the phrase "different quality" are indefinite and without further *de novo* experimentation, the skilled artisan allegedly would not be able to predict which synonymous codons to replace in a parent nucleotide in order to confer an immune response of a "different quality" to a target antigen. Applicant respectfully traverses.

The claims have been amended to specify that the immune response is of a selected class and that the parent polynucleotide is modified by inclusion of synonymous codons that exhibit a different preference for conferring the immune response of the selected class than the codons they replace; the synthetic polynucleotide so produced confers an immune response of the selected class in a different strength, intensity or grade than that conferred by the parent polynucleotide.

The Federal Circuit recently addressed the written description requirement of §112, first paragraph, in detail, stating that:

> "The law must be applied to each invention at the time it enters the patent process, for each patented advance has a novel relationship with the state of the art from which it emerges."

See Ariad Pharmaceuticals, Inc. v Eli Lilly & Co. (Fed. Cir. 2010) (*en banc*) (hereafter "*Ariad*"). This statement reiterates the court's earlier holding that:

> "The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge."

Capon v Eshhar, 418 F. 3d 1349 (Fed. Cir. 2005) The Court's decision in *Ariad* further confirmed its earlier holding that:

(a) Examples are not necessary to support the adequacy of a written description; and

(b) The written description standard may be met even where actual reduction to practice of an invention is absent; in other words, a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.

Falko-Gunter Falkner v Inglis 448 F. 3d 1357, 1366-67 (Fed. Cir. 2006). Applicant respectfully submits that the specification provides ample disclosure that demonstrates that applicant was fully in possession of the claimed invention in the context of the state of the knowledge at the time the application was filed.

Claim 39 as amended recites a method for constructing a synthetic polynucleotide from which a polypeptide is producible to confer an immune response of a selected class to a target antigen in a mammal of interest, where that response is in a different strength, intensity or grade than that conferred by a parent polynucleotide that encodes the same polypeptide. This method comprises the following steps:

> (a) selecting a codon of the parent polynucleotide for replacement with a synonymous codon, *wherein the synonymous codon is selected on the basis that it exhibits a different preference for conferring an immune response of the selected class than the first codon in a comparison of preferences of individual synonymous codons for conferring an immune response of the selected class* in test mammals…..; and
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> (b) replacing the first codon with the synonymous codon to construct the synthetic polynucleotide.

[Emphasis added]. In other words, the method of claim 39 is directed to changing the strength, intensity or grade of immune response of the selected class that is conferred by a polynucleotide of interest (*i.e.*, the parent polynucleotide) based on replacing one or more codons in that polynucleotide with ones that have a higher or lower preference for conferring an immune response of the selected class. The codon replacement thus requires knowledge of an individual codon's preference for conferring the immune response of the selected class (*e.g.*, an antibody response to a target antigen) relative to the preference of other synonymous codons for conferring the same immune response. The specification provides ample guidance to a person of ordinary skill in the art with respect to how to establish these comparisons, how to make suitable codon replacements in a parent polynucleotide, and how to thereby construct a synthetic polynucleotide from which the encoded polypeptide is producible to confer an immune response of the selected class in a different strength, intensity or grade than that conferred by the parent polynucleotide.

Specifically, the specification discloses an illustrative example of a synthetic construct system for assessing the preference of synonymous codons for conferring a phenotype of interest (*see*, discussion in paragraphs [0055] – [0060]). This construct system was previously disclosed in WO 00/42215 for assessing the translational efficiencies of different synonymous codons in specific cell types where the levels of reporter protein expressed in those cell types are sensitive to the intracellular abundance of the iso-tRNA species corresponding to the codon being interrogated. In contrast to WO 00/42215, however, the present specification how such a construct system can be used to determine the influence of a particular codon on a phenotype or class of phenotype (*e.g.*, an immune response of a selected class) that is displayed by an organism (*e.g.*, a mammal) and to compare the phenotypic preferences of different synonymous codons.

The instant specification further outlines how such a construct system can be introduced into a cell or tissue type of test organism (*see*, paragraph [0065]) using a particular route of administration (*e.g.*, oral, parenteral, mucosal or dermal route). Several illustrative methods are also provided for introducing the construct system into cells or tissues including chemical methods, physical methods, vector-based methods and receptor mediated methods, as noted in paragraph [0066].

The specification further teaches how to determine the quality (*e.g.*, strength, intensity or grade) of the selected phenotype (*e.g.*, an immune response of a selected class) by suitable assay and how to compare the phenotypes displayed by individual test organisms to determine the relative preference of each synonymous codon for conferring the phenotype

(*see*, paragraph [0068]). Several art recognised assays for assaying an immune response of a selected type are disclosed in paragraph [0069], including direct measurement of peripheral blood lymphocytes; natural killer cell cytotoxicity assays, cell proliferation assays, immunoassays of immune cells and subsets, and sink tests for cell-mediated immunity.

The specification then further describes how a person of skill in the art can compare the qualities (*e.g.*, the strength, intensity or grade) of the selected phenotype (*e.g.*, immune response of a selected class) displayed by the test organisms to provide a ranked order of individual synonymous codons according to their preference of usage by the test organisms to confer the selected phenotype. In this way, the specification clearly teaches methods for a person of ordinary skill in the art to determine a "codon preference table" that compares the preference of each synonymous codon to the preference of other synonymous codons for conferring the selected phenotype.

Further guidance in the specification instructs the skilled artisan in how codons in a particular parent polynucleotide can be selected for replacement with a synonymous codon which has either a higher or lower preference for conferring the selected phenotype (*see*, paragraphs [0071] – [0077]) in order to produce a codon modified, synthetic polynucleotide that confers the selected phenotype (*e.g.*, an immune response of a selected type) in a different quality (*e.g.*, strength, intensity or grade) than the parent polynucleotide.

Finally, the specification also provides a prophetic method for determining the preference of different synonymous codons for conferring an antibody response to a target antigen (*see*, Example 1 on pages 29-30). Moreover, applicant has provided declaratory evidence to establish that the teachings in the present specification can be followed to prepare a series of expression constructs, to immunise test mice with these constructs, to measure antibody titers against the target antigen resulting from the immunisations and to subsequently derive a codon preference table for modulating the antibody response to antigen in mammals. These results are also disclosed in WO 2009/049350, a copy of which is appended to Professor Frazer's supplemental Declaration, submitted herewith.

For the reasons discussed above, applicant respectfully submits that the specification provides ample evidence that he was fully in possession of the claimed invention at the time of filing, and that claims 31-44, 46-58 and 77-78 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of the rejection respectfully is requested.

Rejection Under 35 U.S.C.§ 112 First Paragraph (Enablement)

Claims 39-44, 46-58 and 77-78 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner alleges that it is not clear if the experiments and results described in Professor Frazer's earlier declaration with respect to the design of a synthetic polynucleotide to produce an improved immune response in a mammal against an HPV E7 protein followed the description present in the specification as filed. Applicant respectfully traverses, since the method used to rank synonymous codons according to their preference for conferring an antibody immune response (this ranking is referred to hereafter as the "antibody Coricode"), and discussed in Professor Ian Frazer's Declaration of record, is indeed broadly based upon the teachings of the instant specification.

Applicant respectfully submits that the Declaration of record refers to a construct system (hereafter referred to as the "Series II construct system") that is structurally different than, but functionally the same as, the one disclosed in the instant specification (hereafter referred to as the "Series I construct system"). In this regard, the Series I construct system uses stretches of identical codons fused in-frame with a reporter polynucleotide (*e.g.*, one that encodes an antigen of interest), whilst the Series II construct system uses the same codon in the reporter polynucleotide to code for every instance a particular amino acid is used in an encoded antigen of interest. Despite these structural differences, however, the Series I and II construct systems are functionally similar as described below.

The only other structural difference between the construct systems is that the Series II vectors referred to in the Declaration of record employ a secretory sequence to enhance antibody titers to the E7 protein. As explained in Professor Ian Frazer's supplemental Declaration, submitted herewith, it was known before the filing date of the present application that antibody responses to antigens could be improved by targeting an antigen of interest to the classical secretory pathway (*see*, for example, Rush *et al.*, *J. Immunol.* 2002, Nov 1; 169: 4951-4960, a copy of which is appended to Professor Frazer's supplemental Declaration).

Professor Frazer's in his supplemental Declaration describes that Series I constructs have been prepared comprising the following structure:

Secretory CDS – XXGXGXX – E7 CDS

wherein:

Secretory CDS is the same secretory coding sequence as the one used in the Series II constructs for targeting the E7 protein to the classical secretory pathway, and

X is the codon whose antibody immune response preference is being interrogated; and

G is glycine and is used as a spacer codon as taught in paragraphs [0058] – [0060] of the present specification for alleviating protein instability (*see*, in particular, paragraph [0059], option (f), and paragraph [0060], which contemplate the XXGXGXX motif.

The supplemental declaration also presents a table that compares the relative preferences of various synonymous codons for conferring an antibody immune response, as obtained using the Series I constructs defined above. Professor Frazer describes how this comparison accords with the one (*i.e.*, the antibody Coricode) obtained using the Series II vectors.

Furthermore, the supplemental declaration explains that the antibody Coricode can be used to modulate the antibody immune response to any antigen of interest and references. In particular, Example 12 of WO 2009/049350, shows that wild-type coding sequences for HPV E7 and HSV gD2 that are modified to include synonymous codons with higher preferences for conferring an antibody immune response than the codons they replace, can elicit higher antibody titers in immunized animals than the wild-type sequences.

As such, it is respectfully submitted that the instant specification clearly enables a person of ordinary skill in the art to make and use the claimed invention without undue experimentation. The Examiner is respectfully urged, therefore, to reconsider and withdraw the enablement rejection.

SUMMARY

In view of the foregoing amendments, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-2283. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).**

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Respectfully submitted,

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